PATENT
Customer Number 22,852
Attorney Docket No. 4012.0188-02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

PRIEELS, J.P. et al.

Serial No.: 08/909,879

Filed: August 12, 1997

For: VACCINE COMPOSITION CONTAINING ADJUVANTS

Group Art Unit: 1648

Examiner: R. Budens

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

REPLY BRIEF

This Reply Brief responds to the Examiner's Answer of January 17, 2001, which is in response to the Appellant's Brief on Appeal and Request for Reconsideration filed concurrently on June 29, 2000. The only rejection before the Board is under 35 U.S.C. § 112, ¶ 1. Contrary to the Examiner's opinion, Appellants have more than met their statutory burden and request the Board to withdraw the rejection.

I. Legal Standard

A specification meeting the requirements of §112, ¶ 1 will "enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use" the invention. 35 U.S.C. § 112, ¶ 1 (1994). In the pharmaceutical and vaccine arts, inventors may, in the appropriate circumstance, rely on animal testing to meet the

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

enablement and utility requirements. For purposes of utility[1], the MPEP directs Examiners to consider factors

> including the test parameters, choice of animal, relationship of the activity to the particular disorder to be treated, characteristics of the compound or composition, relative significance of the data provided and, most importantly, the explanation offered by the applicant as to why the information provided is believed to support the asserted utility. **If the data supplied is consistent with the asserted utility, the Office cannot maintain a rejection under 35 U.S.C. 101**.

M.P.E.P. § 2107.02 (emphasis added).The MPEP further instructs that:

> [d]ata from any test that the applicant reasonably correlates to the asserted utility should be evaluated substantively. Thus, an applicant may provide data generated using a particular animal model with an appropriate explanation as to why that data supports the asserted utility. The absence of a certification that the test in question is an industry-accepted model is not dispositive of whether data from an animal model is in fact relevant to the asserted utility. *Id.*

Thus, if one skilled in the art would accept the animal tests as being reasonably predictive of utility in humans, evidence from those tests should be considered sufficient to support the credibility of the asserted utility. Indeed, the key question is whether "one skilled in the art would accept the animal tests as being reasonably predictive of utility in humans." *Id.*[2] Examiners are not permitted to find evidence unpersuasive "simply because no animal model for the human disease condition had been established prior

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[1] In Note 16 in Appellants' Brief, Appellants discuss how utility requirements in the pharmaceutical arts are closely related to enablement.

[2] Footnote 54 of Appellants' Brief discusses the Federal Circuit's interpretation of the *in vitro* to *in vivo* correlation standard and how Appellants have more than met this standard by introducing *in vivo* evidence using the SHIV/macaque model.

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

to the filling of the application." *Id.* Finally, Examiners "should not impose on applicants the unnecessary burden of providing evidence from human clinical trials." *Id.*

In sum, the most important evidence the Office considers comes from Appellants; and, such evidence need not include human clinical trials. As shown below, Appellants clearly meet this standard.

II. Appellants' Meet the Requirements of 35 U.S.C. § 112 ¶1

The Appellants' uncontested evidence conclusively establishes that the claimed vaccines prevented infection in ten of twelve macaques challenged with SHIV (the SHIV/macaque model). No vaccine is 100% effective in all cases and it is not Appellants burden to prove 100% efficacy in order to obtain patent rights to a vaccine. That the claimed vaccine was effective in ten of twelve tries remains uncontroverted and provides overwhelming evidence of efficacy for enablement purposes. The Examiner contends, however, that the use of the SHIV/macaque model does not correlate with expected results in humans. He cites to Joag, an article relied upon by the Appellants, for the proposition that the HIV/chimpanzee model is more biologically relevant than the SHIV/macaque model. *Id.* What the Examiner fails to note however, is that Joag specifically states that vaccines having the gp120 antigen, an antigen included within the claimed invention, "can be extrapolated to humans with a high level of confidence as biological differences are absent or insignificant." (Exhibit 8 , Table II, p. 225).[3] A closer look at Joag reveals that the Examiner's position is overly general and, moreover,

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

[3] All Exhibit references are directed to the Exhibit Book which accompanied Appellants' Brief of June 29, 2000. A duplicate copy is provided together with this Reply Brief for the Board's convenience.

irrelevant. Table II on page 225 of Joag shows that with non-antigen therapies such as in live vaccines or drug treatment, the chimpanzee model correlates better to humans than SHIV/macaque. The claimed invention, however, does not claim these modalities. Thus, the Examiner's argument is irrelevant and fails to establish that Appellants' SHIV/macaque model is not reasonably predictive of utility and enablement in humans.

The Examiner's belief that no animal model whatsoever suffices is similarly flawed. The key issue here is whether vaccines of the claimed invention are *reasonably* correlated in humans. The evidence before the Board in the form of declarations from Dr. Voss as well as the Mooij and Joag articles show that the Appellants' invention meets the statutory requirements, and the Examiner has set forth no evidence that Appellants' claimed vaccine is either ineffective or fails to correlate in humans.

III. The Examiner's Arguments are Flawed Legally and Factually

A. The Examiner's Answer Contradicts PTO Rules and Guidelines

Contrary to Patent Office rules, the Examiner argues that an art-recognized model is necessary for an enabling disclosure. The Examiner states that, "[t]o date, no HIV vaccine has been shown to be effective in humans and, therefore, one skilled in the art cannot make the appropriate correlations between animal models of HIV and the probable results in human therapy as required by the courts." (Page 6 of Examiner's Answer). This position starkly contradicts MPEP guidelines as discussed above. "The MPEP does not have the force and effect of law; however, it is entitled to judicial notice as the agency's official interpretation of statutes or regulations, provided that it is not in conflict with the statutes or regulations." *Refac International Ltd. v. Lotus Development Corp.*, 38 U.S.P.Q. 2d 1665, 1671 n.2 (Fed. Cir. 1996) (citations omitted). The Examiner

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

should not be permitted to unilaterally contravene PTO policy, remove the "reasonably predictive" MPEP standard, and forbid Appellants from relying on animal data to show human correlation.

In another legal error, the Examiner cites the supposed need for human clinical trials in order to develop an enabling vaccine. Quoting Haynes, the Examiner's Answer states, "lacking these [animal] models, researchers must turn towards human clinical trials to answer many of the difficult questions about HIV pathogenesis and HIV vaccine development." (Page 8 of Examiner's Answer). The Examiner also explicitly states:

> It is the Examiner's position that not only cannot appellants' animal model be shown to reasonably correlate with *in vivo* efficacy in humans, but that, to date, no animal model for HIV vaccines has shown to correlate with efficacy in humans.

(Page 9 of Examiner's Answer). By rejecting all animal data and, presumably, *in vitro* data, the Examiner is effectively requiring human clinical data even though, as discussed above, there is an animal model that is reasonably predictive of utility and enablement in humans. Such a position has no legal basis and the MPEP specifically and unequivocally forbids it. "Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials." M.P.E.P. § 2107.02.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

B. The Examiner's Answer is Based on Unsubstantiated Evidence

The Examiner should not also be permitted to make assertions without providing supporting evidence. The Examiner now states that, "[t]here are many researchers working hard with many *in vitro* and *in vivo* systems and animal models trying to find answers to a terrible viral infection." (Page 9 of the Examiner's Answer). The Examiner does not state that the SHIV/macaque model or Appellants' vaccine was involved in any of these tests. Absent such evidence, the Examiner's remarks are simply irrelevant and the Examiner's reliance on this unsubstantiated evidence is unfair to Appellants. This glaring omission is indicative of the Examiner's tact which is to avoid discussing specifics of the Appellants' antigen anti-HIV vaccine and instead rely on broad overgeneralizations that never rebut what Appellants claim.

Indeed, the quote relied upon by the Examiner from *In re Hartop*, 135 USPQ 419 (C.C.P.A. 1962), makes the point for Appellants. It states that "inherent in the concept of the 'standard experimental animal' is the ability of one skilled in the art to make the appropriate correlations between the results actually observed with the animal experiments and the probable results in human therapy." *Id.* at 426. The declaration of Voss and the article by Joag show that the SHIV/macaque model, especially with antigen vaccines, are expected to reasonably correlate to humans.

C. The Examiner's References Fail to Rebut Appellant's Evidence that the SHIV/macaque Model is Reasonably Predictive

The evidence and arguments set forth by the Examiner do not render the instant claims non-enabled. The Examiner continues to maintain that obstacles to therapy of HIV are "well documented in the literature." (Pages 4-5 of Examiner's Answer).

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

However, therapies, such as protease inhibitors, are known to treat HIV infection. Furthermore, in Appellant's brief on pages 14 and 15, several of these obstacles were shown to exist with other disease conditions in which Appellants received patent claims in the parent case. The Examiner should not equate "obstacles" with "impossible" as Appellants' data shows the invention works on the SHIV/macaques model - a fact that remains unrefuted.

On page 5 of the Examiner's Answer, the Examiner discusses the art cited during prosecution. Foremost among these is Haynes et al. which the Examiner cites three times. Haynes does not, however, discuss the SHIV/macaque model and instead only mentions animal models related to SIV and HIV not SHIV/macaque. Thus, the Examiner's reliance on Haynes is misguided. Likewise, none of the other references relied upon by the Examiner mentions the SHIV/macaque model and the claimed vaccine.

Compounding the error, as noted above, the Examiner flatly ignores key elements of Joag and the Voss declarations. Joag explicitly states that SHIV/macaque model results for gp120 vaccines "can be extrapolated to humans with a high level of confidence as biological differences are absent or insignificant." (Exhibit 8, table II, p. 225). By comparison, the Examiner relies on unsupported arguments that the general public, a group that is not representative of one of ordinary skill in the art, watches nightly television programs reporting on the failure of vaccine AIDS research. Nowhere does the Examiner provide even a shred of evidence that these so called reports relate to Appellants' claimed vaccine. This unsubstantiated argument is symptomatic of the Examiner's entire Answer which incorrectly applies MPEP guidelines and fails to

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

counter any of Appellants' evidence regarding either the efficacy or the correlation expected between Appellants' SHIV/macaque data and humans.

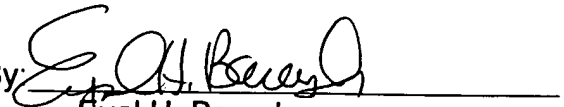
IV. Conclusion

The SHIV/macaque model used by Appellants has shown that the claimed vaccine protected ten of twelve macaques after challenge. This dramatic evidence of efficacy meets the statutory enablement requirement in view of the declarations by Dr. Voss, and the Joag article demonstrating that in the context of the vaccines of the claimed invention, the rhesus macaque data should be viewed as correlative in humans. Accordingly, Appellants respectfully request that all pending claims be allowed.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: March 15, 2001

By: 

Eyal H. Barash
Reg. No. 43,483

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000